REMARKS

The present claim amendments embody the working examples in the specification, which may be summarized as follows.

TABLE 1

		1 2 3 4 5			5	
	Examples	Unit Dose	Nebulizer/	Aerosol	Emitted Dose	Duration of
	_	Concentration	Compressor	Output	Efficiency	Nebulization
		Volume		Tl/sec	%	min
A	1 and 2	60 mg/ml 5 ml	Pari LC Plus/ PulmoAide @ 20 psi	3.8 3.3 (Ex. 2)	26	17.7 20.4 (Ex. 2)
	·	60 mg/ml 0.5 ml	Aerodose	6.0	68	2.8
		60 mg/ml 1.0 ml	Aerodose	6.4	68	5.2
		60 mg/ml 1.5 ml	AeroDose	6.2	68	8.0
В	3	60 mg/ml 5 ml	Pari LC Plus/ PulmoAide @ 20 psi	3.7	'control'	18.1
		120 mg/ml 3.5 ml	Pari LC Plus/ Mobilaire @ 35 psi	6.9	'experimental'	9.7

Notes to Table 1:

A1 and A2. See page 15, lines 1 to 8, and page 65, lines 3 to 7. The control system, *Pari LC Plus/PulmoAide* @ 20 psi, refers to the current conventional delivery system; see page 5, lines 3 to 14, and IDS documents O1 and A.

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A3. Aerosol output is calculated in Tl/sec by dividing the Unit Dose Volume, minus the residual (dead space) volume of the nebulizer, by the Nebulization Time Period. For the Pari LC Plus nebulizer a residual volume of 1 ml is conservatively assumed; see IDS document A at Col. 8, lines 17 to 19, and particularly IDS document O2 at Table 2, row 1. In contrast, the AeroDose nebulizes almost the entire drug dose that is placed in the unit; see the later published IDS document O23 at page 34, right column, second paragraph. Because the AeroDose device is breath actuated, the above-described aerosol output calculation was doubled, on the basis that the aerosolization did not occur during approximately one-half of the duration of nebulization time period.

A4. See page 71, lines 13 to 15.

<u>A5</u>. See page 49, lines 15 to 21.

<u>B1 and B2</u>. See page 75, lines 3 to 13.

B3. See note A3.

<u>B4</u>. For 'control' efficiency see note A4. For 'experimental' see page 92, lines 1 to 7.

B5. See page 92, lines 9 to 16.

Referring to Table 1 above, Example 3 demonstrated that nebulization time for the test 420 mg formulation was substantially reduced below that observed for the marketed 300 mg TOBI[®] formulation— without changing the pharmokinetics of antibiotic delivery. This study achieved the key benchmark of reduced nebulization time below 10 minutes on the average. (See page 94, lines 7 to 19.)

Thus, Claim 1 has been amended to recite the constellation of parameters, including relatively low unit dose volumes (4.0 ml or less), relatively high unit dose concentrations (about 60 to about 200 mg/ml), and relatively high aerosol outputs (not less than about 4 Tl/sec), requisite to achieve this remarkably short duration of nebulization (less than about 10 minutes).

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Examples 1 and 2 demonstrated that, moreover, the emitted dose efficiency can be substantially increased without substantial impairment of clinical outcome. Dependent Claims 20 to 23 are directed to such embodiments.

Dependent Claim 27 specifies that at least 20 mg of tobramycin is delivered to the patient, as disclosed at page 71, lines 6-12.

Independent Claim 28 is directed to a preferred embodiment of the present invention.

Thus, by the more efficient administration of tobramycin formulations provided by the claimed invention, substantially smaller volumes of tobramycin than the conventional administration regime are administered in substantially shorter periods of time, thereby reducing the costs of administration and drug wastage, and significantly enhancing the likelihood of patient compliance. (See page 8, line 29, to page 9, line 4.)

INFORMATION DISCLOSURE STATEMENT

The following Table 2 summarizes the disclosures of the documents listed in the contemporaneously filed form PTO-1449.

TABLE 2

IDS	Antibiotics	Unit Dose	Nebulization
Citation	Chemical class	Concentration	Time
No.	generic name	Volume	Minutes
O1	Aminoglycoside	60 mg/ml	~15
4/01	tobramycin	5 ml	
O2	Aminoglycoside	60 mg/ml	7.9-20.9
2000	tobramycin	5 ml	
O3	Aminoglycoside	Not reported	≤ 5-10
3/2/00	tobramycin		
O4	Aminoglycoside	20 mg/ml	10.3-18.7
1999	tobramycin	4 ml	

IDS	Antibiotics	Unit Dose	Nebulization
Citation	Chemical class	Concentration	Time
No.	generic name	Volume	Minutes
В	Aminoglycosides	4-100 mg/ml	
1998	gentamicin	1-5 ml	
	amikacin		
	kanamycin		
	streptomycin		
	neomycin		
	netilmicin		
	tobramycin		
	Macrolide	20/1	10-12
	erythromyclamide	20 mg/ml 30 ml	10-12
		30 1111	
		60 mg/ml	10-13
		5 ml	10 13
F1	Same as B	Same as B	Same as B
05			See Fig. 4
1997			
O6	Aminoglycoside	26.7 mg/ml	6-8
1997	tobramycin	3 ml	
O7	<u>Aminoglycosides</u>		Not reported
1997	tobramycin	20, 50, 100, and 200	
Smith		mg/ml	
		20 1 40 /1	
	gentamicin	20 and 40 mg/ml	
	Beta-lactam		
	ceftazidime	50, 100, 250, and 500	
		mg/ml	•
		6	
	Quinolone		
	ciprofloxacin	<u>10 mg/ml</u>	
	<u>Polymoxin</u>		
	colistin	5, 50, and 75 mg/ml	
08	Aminoglycoside	60 mg/ml	≥ 15
1997	tobramycin	10 ml	

IDS	Antibiotics	Unit Dose	Nebulization
Citation	Chemical class	Concentration	Time
No.	generic name	Volume	Minutes
U1	<u>Aminoglycoside</u>	8-160 mg/ml	
1996	tobramycin	1-5 ml	
		20 mg/ml	10-12
		30 ml	
		(0 / 1	10.12
		60 mg/ml	10-13
EO	Comp on III	5 ml	O TI1
F2 O9	Same as U1	Same as U1	Same as U1
1996	Aminoglycoside Tobramycin	50 mg/m1	10 minute sessions
1990	Tobramycin	50 mg/ml 1.5-12 ml	
	Polymoxin	1.3-12 1111	
	colistine	11.1 mg/ml	
	Constine	3-12 ml	
O10	Aminoglycoside	20 mg/ml	Not reported
1996	tobramycin	4 ml	riot reported
	1001411170111	· · · · · · · · · · · · · · · · · · ·	
		40 mg/ml	
		2 ml	
		75 mg/ml	
		1.1 ml	
011	Aminoglycoside	666 ∀ 195 mg	200 inspirations
1995	tobramycin		
Smith			
A ('269)	<u>Aminoglycosides</u>	40-100 mg/ml	Not reported ¹
1994	gentamicin	5 ml	
Smith	tobramycin		
012	Aminoglycoside	20 mg/ml	Not reported
1994	tobramycin	20 1	
Smith		30 ml	
		1 m1	
L		4 ml	

 $^{^{1}}$ Attached is a Declaration of Arnold Smith, M.D., which discusses the $\underline{\text{in}}$ $\underline{\text{vitro}}$ "Time to Nebulize" measurements listed in Table 1 of the '269 patent.

IDS	Antibiotics	Unit Dose	Nebulization
Citation	Chemical class	Concentration	Time
No.	generic name	Volume	Minutes
O13	Aminoglycoside	7.5 mg/kg/dose	60
1994	tobramycin	mean = 266 mg	
O14	Aminoglycosides	4 ml	10-20
1993	gentamicin	40-160 mg	
	tobramycin	40-160 mg	
	amikacin	250-500 mg	
	neomycin		
	Polymoxin		
	colistin	0.5-1 mg	
	Beta-lactams		
	ceftazidime		
	carbenicillin		
	ticarcillin		
	cephaloridine		
	cloxacillin		
	methicillin		
	<u>Antifungal</u>		
	amphotericin	10 mg	
O15	Aminoglycoside	150 mg/ml	~5
Le Conte	tobramycin	2 ml	
1993			
O16	Aminoglycoside	50 mg/ml	200 tidal
1993	tobramycin	30 ml	inspirations
Smith			
O17	<u>Aminoglycoside</u>	0.35 mg/ml	10-minute sessions
1993	tobramycin	2 ml	(to guinea pigs)
O18	<u>Aminoglycoside</u>	10 mg/ml	15
1991	tobramycin		(to rats)
O19	<u>Aminoglycoside</u>	20 mg/ml	200 inhalations
1989	tobramycin	30 ml	
Smith			
O20	<u>Aminoglycoside</u>	40 mg/ml	≥ 15
1989	tobramycin	2 ml	
O21	<u>Aminoglycoside</u>	80 mg	Not reported
1989	tobramycin	2 ml	
O22	Adrenergic agents	\leq 0.3 ml of 0.5 %	15- 20 minutes
1988	(for asthma)	solution	
		0.5 % solution	5 inspirations

LAW OFFICES OF CHRISTENSEN O'CONNOR JOHNSON KINDNESS^{PLLC} 1420 Fifth Avenue Suite 2800 Seattle, Washington 98101 206.682.8100 Referring to the above Table 2, several of the listed documents disclose nebulization

times of about 10 minutes or less, but none read on the constellation of parameters recited in the

present claims, as summarized below.

O2 evaluated the standard 5 ml tobramycin, 60 mg/ml, with the Pari LC Plus nebulizer

using various compressors. Table 2 indicates that the faster compressors (Nebulization time)

were less efficient (Residual volume) that the standard PulmoAide compressor.

O3 simply discloses a goal to reduce Tobi's delivery time of 15 to 20 minutes to 5 to 10

minutes or less.

O4 discloses a relatively dilute tobramycin solution of 20 mg/ml.

B discloses, in Table 3, delivery of 5 ml erythromyclamide, 60 mg/ml, in 10 minutes

using the Pari LC nebulizer with the PulmoAide compressor.

O6 discloses a relatively dilute tobramycin solution of 26.7 mg/ml.

U1 discloses, in Table 3, delivery of 5 ml tobramycin, 60 mg/ml, in 10 minutes using the

Pari LC nebulizer with the PulmoAide compressor.

O14 discloses that a high flow rate reduces the nebulization time and 10-20 minutes is

suggested as a clinically acceptable range; see page 101, right column.

O15 discloses nebulized delivery of 2 ml tobramycin, 150 mg/ml, to healthy volunteers in

LAW OFFICES OF CHRISTENSEN O'CONNOR JOHNSON KINDNESS**LC 1420 Fifth Avenue Suite 2800

Seattle, Washington 98101 206.682.8100 about 5 minutes. However, the emitted dose efficiency was only 17 percent (page 1281, left column), and lung uptake of the antibiotic was reportedly poor (page 1281, right column).

Respectfully submitted,

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TFB:snh